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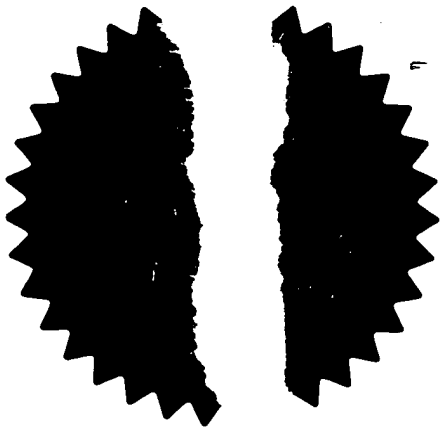

Signed Andrew Gregg

Dated 26 FEB 2002

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2.	Patent application number *(The Patent Office will fill in this part)*	**9828377.3**
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**JANSSEN PHARMACEUTICA N.V.** **TURNHOUTSEWEG 30** **B-2340 BEERSE** **BELGIUM**
	Patents ADP number *(if you know it)*	53193001
	If the applicant is a corporate body, give the country/state of its incorporation	**BELGIUM**
4.	Title of the invention	**VASCULAR ENDOTHELIAL GROWTH FACTOR-E**
5.	Name of your agent *(if you have one)*	**BOULT WADE TENNANT** **27 FURNIVAL STREET** **LONDON** **EC4A 1PQ**
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11. I/We request the grant of a patent on the basis of this application.

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22 December 1998

12. Name and daytime telephone number of person to contact in the United Kingdom

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VASCULAR ENDOTHELIAL GROWTH FACTOR-E

The present invention is concerned with a novel vascular endothelial growth factor (VEGF) herein designated "VEGF-E", and characterisation of the nucleic acid and amino acid sequences of VEGF-E.

Angiogenesis involves formation and proliferation of new blood vessels, and is an essential physiological process for normal growth and development of tissues in, for example, embryonic development, tissue regeneration and organ and tissue repair. Angiogenesis also features in the growth of human cancers which require continuous stimulation of blood vessel growth. Abnormal angiogenesis is associated with other diseases such as rheumatoid arthritis and psoriasis.

Capillary vessels consist of endothelial cells which carry the genetic information necessary to proliferate to form capillary networks. Angiogenic molecules which can initiate this process have previously been characterised. A highly selective mitogen for vascular endothelial cells is vascular endothelial growth factor (VEGF) (Ferrara *et al.*, "Vascular Endothelial Growth Factor: Basic Biology and Clinical Implications". Regulation of angiogenesis, by I.D. Goldberg and E.M. Rosen 1997 Bikhanser Vertag Basle/Switzerland). VEGF is a potent vasoactive protein which is comprised of a glycosylated cationic 46-49 kd dimer having two 24 kd subunits. It is inactivated by sulfhydryl reducing agents and is resistant to acidic pH and to heating and binds to immobilised heparin.

VEGF has four different forms of 121, 165, 189 and 206 amino acids due to alternative splicing. VEGF121 and VEGF165 are soluble and are capable of promoting angiogenesis, whereas VEGF189 and VEGF206 are bound to heparin containing proteoglycans in the cell surface. The temporal and spatial expression of VEGF has been correlated with physiological proliferation of the blood vessels (Gajdusek, C.M., and Carbon, S.J., Cell Physiol., 139:570-579, (1989)); McNeil, P.L., Muthukrishnan, L., Warder, E., D'Amore, P.A., J. Cell. Biol., 109:811-822, (1989)). Its high affinity binding sites are localized only on endothelial cells in tissue sections (Jakeman, L.B., *et al.*, Clin. Invest. 89:244-253, (1989)). The growth factor can be isolated from pituitary cells and several tumor cell lines, and has been implicated in some human gliomas (Plate, K.H. Nature 359:845-848, (1992)). The inhibition of VEGF function by anti-VEGF monoclonal antibodies was shown to inhibit tumor growth in immune-deficient mice (Kim, K.J., Nature 362:841-844, (1993)).

The present inventors have now identified a further vascular endothelial growth factor, designated herein as "VEGF-E", and the nucleic acid sequence encoding it, which has potentially significant benefits for the treatment of tumours.

Therefore, according to a first aspect of the present invention there is provided a nucleic acid molecule encoding a VEGF-E protein or a functional equvalent, derivative or bioprecursor thereof, said protein comprising the amino acid sequence illustrated in Figure 2 or 4. Preferably, the nucleic acid molecule is a DNA and even more preferably a cDNA molecule.

Also provided by this aspect of the present invention is a nucleic acid molecule such as an antisense molecule capable of hybridising to the nucleic acid molecules according to the invention under high stringency conditions.

Stringency of hybridisation as used herein refers to conditions under which polynucleic acids are stable. The stability of hybrids is reflected in the melting temperature (Tm) of the hybrids. Tm can be approximated by the formula:

$$81.5°C+16.6(\log_{10}[Na^+]+0.41\ (\%G\&C)-6001/l$$

wherein l is the length of the hybrids in nucleotides. Tm decreases approximately by 1-1.5°C with every 1% decrease in sequence homology.

The nucleic acid capable of hybridising to nucleic acid molecules according to the invention will generally be at least 70%, preferably at least 80 or 90% and more preferably at least 95% homologous to the nucleotide sequences according to the invention.

The present invention also comprises within its scope proteins or polypeptides encoded by the nucleic acid molecules according to the invention or a functional equivalent, derivative or bioprecursor thereof.

Therefore, according to a further aspect of the present invention, there is provided a VEGF-E protein, or a functional equivalent, derivative or bioprecursor thereof, having an amino acid sequence as illustrated in Figure 2 or 4. A further aspect of the invention comprises a VEGF-E protein, or a functional

equivalent, derivative or bioprecursor thereof, encoded by a nucleic acid molecule according to the invention. Preferably, the VEGF-E protein encoded by said nucleic acid molecule comprises an amino acid sequence as illustrated in Figure 2 or 4.

The DNA molecules according to the invention may, advantageously, be included in a suitable expression vector to express VEGF-E encoded therefrom in a suitable host.

An expression vector according to the invention includes a vector having a nucleic acid according to the invention operably linked to regulatory sequences, such as promoter regions, that are capable of effecting expression of said DNA fragments. The term "operably linked" refers to a juxta position wherein the components described are in a relationship permitting them to function in their intended manner. Such vectors may be transformed into a suitable host cell to provide for expression of a polypeptide according to the invention. Thus, in a further aspect, the invention provides a process for preparing polypeptides according to the invention which comprises cultivating a host cell, transformed or transfected with an expression vector as described above under conditions to provide for expression by the vector of a coding sequence encoding the polypeptides, and recovering the expressed polypeptides.

The vectors may be, for example, plasmid, virus or phage vectors provided with an origin of replication, optionally a promoter for the expression of said nucleotide and optionally a regulator of the promoter.

The vectors may contain one or more selectable markers, such as, for example, ampicillin resistance.

Regulatory elements required for expression include promoter sequences to bind RNA polymerase and transcription initiation sequences for ribosome binding. For example, a bacterial expression vector may include a promoter such as the lac promoter and for transcription initiation the Shine-Dalgarno sequence and the start codon AUG. Similarly, a eukaryotic expression vector may include a heterologous or homologous promoter for RNA polymerase II, a downstream polyadenylation signal, the start codon AUG, and a termination codon for detachment of the ribosome. Such vectors may be obtained commercially or assembled from the sequences described by methods well known in the art.

Nucleic acid molecules according to the invention may be inserted into the vectors described in an antisense orientation in order to provide for the production of antisense RNA. Antisense RNA or other antisense nucleic acids may be produced by synthetic means.

In accordance with the present invention, a defined nucleic acid includes not only the identical nucleic acid but also any minor base variations including in particular, substitutions in bases which result in a synonymous codon (a different codon specifying the same amino acid residue) due to the degenerate code in conservative amino acid substitutions. The term "nucleic acid sequence" also includes the complementary sequence to any single stranded sequence given regarding base variations.

The present invention also advantageously provides nucleic acid sequences of at least approximately 10 contiguous nucleotides of a nucleic acid according to the invention and preferably from 10 to 50 nucleotides. These sequences may, advantageously be used as probes or primers to initiate replication, or the like. Such nucleic acid sequences may be produced according to techniques well known in the art, such as by recombinant or synthetic means. They may also be used in diagnostic kits or the like for detecting the presence of a nucleic acid according to the invention. These tests generally comprise contacting the probe with the sample under hybridising conditions and detecting for the presence of any duplex or triplex formation between the probe and any nucleic acid in the sample.

The nucleic acid sequences according to this aspect of the present invention comprises the sequences of nucleotides designated herein as VEGFE 1-10, illustrated in Figure 5.

According to the present invention these probes may be anchored to a solid support. Preferably, they are present on an array so that multiple probes can simultaneously hybridize to a single biological sample. The probes can be spotted onto the array or synthesised *in situ* on the array. (See Lockhart *et al.*, Nature Biotechnology, vol. 14, December 1996 "Expression monitoring by hybridisation to high density oligonucleotide arrays". A single array can contain more than 100, 500 or even 1,000 different probes in discrete locations.

The nucleic acid sequences, according to the invention

may be produced using such recombinant or synthetic means, such as for example using PCR cloning mechanisms which generally involve making a pair of primers, which may be from approximately 10 to 50 nucleotides to a region of the gene which is desired to be cloned, bringing the primers into contact with mRNA, cDNA, or genomic DNA from a human cell, performing a polymerase chain reaction under conditions which bring about amplification of the desired region, isolating the amplified region or fragment and recovering the amplified DNA. Generally, such techniques as defined herein are well known in the art, such as described in Sambrook *et al* (Molecular Cloning: a Laboratory Manual, 1989).

The nucleic acids or oligonucleotides according to the invention may carry a revealing label. Suitable labels include radioisotopes such as ^{32}P or ^{35}S, enzyme labels or other protein labels such as biotin or fluorescent markers. Such labels may be added to the nucleic acids or oligonucleotides of the invention and may be detected using known techniques *per se*.

The protein according to the invention includes all possible amino acid variants encoded by the nucleic acid molecule according to the invention including a polypeptide encoded by said molecule and having conservative amino acid changes. Proteins or polypeptides according to the invention further include variants of such sequences, including naturally occurring allelic variants which are substantially homologous to said proteins or polypeptides. In this context, substantial homology is regarded as a sequence which has at least 70%, preferably 80 or 90% amino acid homology with the

proteins or polypeptides encoded by the nucleic acid molecules according to the invention.

The nucleic acid or protein according to the invention may be used as a medicament or in the preparation of a medicament for treating cancer or other diseases or conditions associated with expression of VEGF-E protein.

Advantageously, the nucleic acid molecule or the protein according to the invention may be provided in a pharmaceutical composition together with a pharmacologically acceptable carrier, diluent or excipient therefor.

The present invention is further directed to inhibiting VEGF2 *in vivo* by the use of antisense technology. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the mature protein sequence, which encodes for the protein of the present invention, is used to design an antisense RNA oligonucleotide of from 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple-helix - see Lee *et al.* Nucl. Acids Res., 6:3073 (1979); Cooney *et al.*, Science, 241:456 (1988); and Dervan *et al.*, Science, 251: 1360 (1991), thereby preventing transcription and the production of VEGF2. The antisense RNA oligonucleotide hybridises to the mRNA *in vivo* and blocks translation of an mRNA molecule into the VEGF2 (antisense - Okano, J. Neurochem., 56:560 (1991); Oligodeoxynucleotides as

Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)).

Alternatively, the oligonucleotide described above can be delivered to cells by procedures in the art such that the anti-sense RNA or DNA may be expressed *in vivo* to inhibit production of VEGF-E in the manner described above.

Antisense constructs to VEGF-E, therefore, may inhibit the angiogenic activity of the VEGF-E and prevent the further growth or even regress solid tumours, since angiogenesis and neovascularization are essential steps in solid tumour growth. These antisense constructs may also be used to treat rheumatoid arthritis, psoriasis and diabetic retinopathy which are all characterized by abnormal angiogenesis.

A further aspect of the invention provides a host cell or organism, transformed or transfected with an expression vector according to the invention. The host cell or organism may advantageously be used in a method of producing VEGF-E, which comprises recovering any expressed VEGF-E from the host or organism transformed or transfected with the expression vector.

According to a further aspect of the invention there is also provided a transgenic cell, tissue or organism comprising a transgene capable of expressing VEGF-E protein according to the invention. The term "transgene capable of expression" as used herein means a suitable nucleic acid sequence which leads to expression of VEGF-E or proteins having the same function and/or activity. The transgene, may include, for example, genomic nucleic acid isolated from human

cells or synthetic nucleic acid, including DNA integrated into the genome or in an extrachromosomal state. Preferably, the transgene comprises the nucleic acid sequence encoding the proteins according to the invention as described herein, or a functional fragment of said nucleic acid. A functional fragment of said nucleic acid should be taken to mean a fragment of the gene comprising said nucleic acid coding for the proteins according to the invention or a functional equivalent, derivative or a non-functional derivative such as a dominant negative mutant, or bioprecursor of said proteins. For example, it would be readily apparent to persons skilled in the art that nucleotide substitutions or deletions may be used using routine techniques, which do not affect the protein sequence encoded by said nucleic acid, or which encode a functional protein according to the invention.

VEGF-E protein expressed by said transgenic cell, tissue or organism or a functional equivalent or bioprecursor of said protein also form part of the present invention.

Antibodies to the protein or polypeptide of the present invention may, advantageously, be prepared by techniques which are known in the art. For example, polyclonal antibodies may be prepared by inoculating a host animal, such as a mouse, with the polypeptide according to the invention or an epitope thereof and recovering immune serum. Monoclonal antibodies may be prepared according to known techniques such as described by Kohler R. and Milstein C., Nature (1975) 256, 495-497.

Antibodies according to the invention may also be used in a method of detecting for the presence of a polypeptide according to the invention, which method comprises reacting the antibody with a sample and identifying any protein bound to said antibody. A kit may also be provided for performing said method which comprises an antibody according to the invention and means for reacting the antibody with said sample.

Proteins which interact with the polypeptide of the invention may be identified by investigating protein-protein interactions using the two-hybrid vector system first proposed by Chien *et al* (1991).

This technique is based on functional reconstitution in vivo of a transcription factor which activates a reporter gene. More particularly the technique comprises providing an appropriate host cell with a DNA construct comprising a reporter gene under the control of a promoter regulated by a transcription factor having a DNA binding domain and an activating domain, expressing in the host cell a first hybrid DNA sequence encoding a first fusion of a fragment or all of a nucleic acid sequence according to the invention and either said DNA binding domain or said activating domain of the transcription factor, expressing in the host at least one second hybrid DNA sequence, such as a library or the like, encoding putative binding proteins to be investigated together with the DNA binding or activating domain of the transcription factor which is not incorporated in the first fusion; detecting any binding of the proteins to be investigated with a protein according to the invention by detecting for the presence of any reporter gene product in the host cell; optionally isolating second

hybrid DNA sequences encoding the binding protein.

An example of such a technique utilises the GAL4 protein in yeast. GAL4 is a transcriptional activator of galactose metabolism in yeast and has a separate domain for binding to activators upstream of the galactose metabolising genes as well as a protein binding domain. Nucleotide vectors may be constructed, one of which comprises the nucleotide residues encoding the DNA binding domain of GAL4. These binding domain residues may be fused to a known protein encoding sequence, such as for example the nucleic acids according to the invention. The other vector comprises the residues encoding the protein binding domain of GAL4. These residues are fused to residues encoding a test protein. Any interaction between polypeptides encoded by the nucleic acid according to the invention and the protein to be tested leads to transcriptional activation of a reporter molecule in a GAL-4 transcription deficient yeast cell into which the vectors have been transformed. Preferably, a reporter molecule such as ß-galactosidase is activated upon restoration of transcription of the yeast galactose metabolism genes.

Advantageously, the antibody according to the invention may also be used as a medicament or in the preparation of a medicament for treating tumours or other diseases associated with expression of VEGF-E. The invention also further provides a pharmaceutical composition comprising said antibody together with a pharmaceutically acceptable carrier diluent or excipient therefor.

A further aspect of the present invention also

provides a method of identifying VEGF-E in a sample, which method comprises contacting said sample with an antibody according to the invention and monitoring for any hybridisation of any proteins to said antibody. A kit for identifying the presence of VEGF-E in a sample is also provided comprising an antibody according to the invention and means for contacting said antibody with said sample.

The invention may be more clearly understood with reference to the accompanying example, which is purely exemplary, with reference to the accompanying drawings, wherein:

Figure 1: is a nucleotide sequence coding for a partial VEGF-E protein according to the invention.

Figure 2: is an illustration of amino acid sequence of the nucleic acid sequence of Figure 1.

Figure 3: is an illustration of a nucleotide sequence encoding VEGF-E protein according to the invention.

Figure 4: is an illustration of the amino acid sequence of the nucleic acid sequence of Figure 3.

Figure 5: depicts the nucleic acid sequences of the first 18 human EST clones obtained from the BLAST search of the LifSeq™ database.

Figure 6: depicts the nucleotide sequences of 50 human EST clones obtained from the proprietary

LifeSeq™ database.

Figure 7: is an illustration of the nucleotide sequences utilised as primers to identify the sequence of the gene coding for VEGF-E.

EXAMPLE 1

A BLAST (Basic Local Alignment Search Tool; Altschul *et al.*, 1990 J. Mol. Biol. 215, 403-410) search was performed in the propriety LifeSeq™ human EST database (Incyte Pharmaceuticals, Inc., Palo Alto, CA, USA). BLAST produces alignments of both nucleotide and amino acid sequences to determine sequence similarity. Because of the local nature of the alignments, BLAST is especially useful in determining exact matches or in identifying homologues. While it is useful for matches which do not contain gaps, it is inappropriate for performing motif-style searching. The fundamental unit of BLAST algorithm output is the High-scoring Segment Pair (HSP).

Eighteen human EST clones (Figure 5) with high similarity to the previously identified VEGF proteins were identified and a further fifty EST clones (Figure 6) were identified using these sequences as query sequences, allowing us to deduce the putative sequence for the new VEGF-E protein. The sequences obtained were compared to known sequences to determine regions of homology and to identify the sequence as a novel VEGF-E protein. Using the DNA sequence information in the databases we were able to prepare suitable primers having the sequences of VEGFE 1-10 illustrated in Figure 7 for use in subsequent RACE experiments to obtain the complete DNA sequence for the VEGF-E gene.

CLAIMS

1. A nucleic acid molecule encoding a VEGF-E protein or a functional equivalent derivative or bioprecursor thereof, said protein comprising the amino acid sequence illustrated in Figures 2 or 4.

2. A nucleic acid molecule according to claim 1 wherein said nucleic acid is a DNA molecule.

3. A nucleic acid molecule according to claim 1 or 2 wherein said nucleic acid is a cDNA molecule.

4. A nucleic acid molecule according to any of claims 1 to 3 comprising the nucleotide sequence illustrated in Figure 1 or 3.

5. A nucleic acid molecule capable of hybridising to a molecule according to any of claims 1 to 4 under high stringency conditions.

6. A VEGF-E protein, or a functional equivalent, derivative or bioprecursor thereof, having the amino acid sequence illustrated in Figure 2 or 4.

7. A VEGF-E protein, or a functional equivalent, derivative or bioprecursor thereof, encoded by a nucleic acid molecule according to any of claims 1 to 4.

8. A protein according to claim 7, which comprises the amino acid sequence illustrated in Figure 2 or 4.

9. An expression vector comprising a nucleic acid molecule according to any of claims 1 to 4.

10. An expression vector according to claim 9 further comprising a nucleotide sequence encoding a reporter molecule.

11. A nucleic acid molecule according to any of claims 1 to 5 for use as a medicament.

12. Use of a nucleic acid molecule according to any of claims 1 to 5 in the preparation of a medicament for inhibiting angiogenic activity and formation and proliferation of new blood vessels, growth and development of tissues, tissue regeneration and organ and tissue repair or for treating cancer or rheumatoid arthritis or psoriasis or diabetic retinopathy.

13. A pharmaceutical composition comprising a nucleic acid molecule or a protein according to any of claims 1 to 5 or 6 to 8 respectively, together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

14. A host cell or organism transformed or transfected with an expression vector according to claim 9 or 10.

15. A transgenic cell, tissue or organism comprising a transgene capable of expressing a VEGF-E protein according to any of claims 6 to 8.

16. A process for producing a VEGF-E protein according to any of claims 6 to 8, said process comprising transforming a host cell or organism with an expression vector according to claim 9 and 10, and recovering the expressed protein from said host cell or organism.

17. An antibody capable of binding to a protein according to any of claims 6 to 8, which is preferably a monoclonal antibody.

18. An antibody according to claim 17 for use as a medicament.

19. Use of an antibody according to claim 17 in the preparation of a medicament for inhibiting angiogenic activity and formation and proliferation of new blood vessels, growth and development of tissues, tissue regeneration and organ and tissue repair or for treating cancer or rheumatoid arthritis or psoriasis or diabetic retinopathy.

20. A pharmaceutical composition comprising an antibody according to claim 17 together with a pharmaceutically acceptable carrier diluent or excipient therefor.

21. A method of identifying VEGF-E in a sample which method comprises contacting said sample with an antibody according to claim 17 and monitoring for binding of any protein to said antibody.

22. A kit for identifying the presence of VEGF-E in a sample which comprises an antibody according to claim 17 and means for contacting said antibody with said sample.

23. A method of identifying compounds which inhibit angiogenesis which method comprises providing a host cell or organism according to claim 14 or a transgenic

cell, tissue or organism according to claim 15, contacting a test compound with said cell, tissue or organism and monitoring for the presence or absence either of said reporter molecule or VEGF-E.

24. A compound identifiable according to the method of claim 23.

25. A compound according to claim 24 for use as a medicament.

26. Use of a compound according to claim 24 in the preparation of a medicament for inhibiting angiogenic activity and formation and proliferation of new blood vessels, growth and development of tissues, tissue regeneration and organ and tissue repair or for treating cancer, rheumatoid arthritis, psoriasis or diabetic retinopathy.

27. A nucleic acid sequence comprising the nucleotide sequence of any of the sequences identified in Figure 6 or 7.

28. An expression vector comprising a nucleic acid sequence according to claim 27.

29. A host cell transformed or transfected with an expression vector according to claim 28.

30. A method for producing a polypeptide, said method comprising the steps of:

a) culturing the host cell of claim 29 under conditions suitable for expression of the peptide; and

b) recovering the polypeptide from the host cell culture.

```
+3                                                M  N  I  F  L  L  N  L  L  T  E  E  V  R  L  Y
                                                  ]-----------------------------------------------
1   AGGAAATCAA ATTAGGATAA GATTTGTATC TGATGAATAT TTTCCTTCTG AACCTTCTAA CAGAGGAGGT AAGATTATAC
    TCCTTTAGTT TAATCCTATT CTAAACATAG ACTACTTATA AAAGGAAGAC TTGGAAGATT GTCTCCTCCA TTCTAATATG
.....
+3  S  C  T  P  R  N  P  S  V  S  I  R  E  E  L  K  R  T  D  T  I  F  W  P  G  C  L
    ----------------------]-----------------------------------------------------------------
81  AGCTGCACAC CTCGTAACTT CTCAGTGTCC ATAAGGGAAG AACTAAAGAG AACCGATACC ATTTTCTGGC CAGGTTGTCT
    TCGACGTGTG GAGCATTGAA GAGTCACAGG TATTCCCTTC TTGATTTCTC TTGGCTATGG TAAAAGACCG GTCCAACAGA
-2                                                <---------------------------------
.....
+3   L  V  K  R  C  G  G  N  C  A  C  C  L  H  N  C  N  E  C  Q  C  V  P  S  K  V
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161 CCTGGTTAAA CGCTGTGGTG GGAACTGTGC CTGTTGTCTC CACAATTGCA ATGAATGTCA ATGTGTCCCA AGCAAAGTTA
    GGACCAATTT GCGACACCAC CCTTGACACG GACAACAGAG GTGTTAACGT TACTTACAGT TACACAGGGT TCGTTTCAAT
-2  -----------------------------------------------------------------------------------------
.....
+3 T  K  K  Y  H  E  V  L  Q  L  R  P  K  T  G  V  R  G  L  H  K  S  L  T  D  V  A
    -----------------------------------------------------------------------------------------
+1                                                V  S  G  D  C  T  N  H  S  P  T  W  P
                                                  ]-----------------------------------------
241 CTAAAAAATA CCACGAGGTC CTTCAGTTGA GACCAAAGAC CGGTGTCAGG GGATTGCACA AATCACTCAC CGACGTGGCC
    GATTTTTTAT GGTGCTCCAG GAAGTCAACT CTGGTTTCTG GCCACAGTCC CCTAACGTGT TTAGTGAGTG GCTGCACCGG
-2  -----------------------------------------------------------[
.....
+3  L  E  H  H  E  E  C  D  C  V  C  R  G  S  T  G  G
    ----------------------------------------------->
+2                                   V  Q  R  E  H  R  R  I  A  A  S  P  P  A  A  L  A
                                     ]-----------------------------------------------------
+1   W  S  T  M  R  S  V  T  V  C  A  E  G  A  Q  E  D  S  R  I  T  T  S  S  S  C
    -----------------------------------------------------------------------------------------
321 CTGGAGCACC ATGAGGAGTG TGACTGTGTG TGCAGAGGGA GCACAGGAGG ATAGCCGCAT CACCACCAGC AGCTCTTGCC
    GACCTCGTGG TACTCCTCAC ACTGACACAC ACGTCTCCCT CGTGTCCTCC TATCGGCGTA GTGGTGGTCG TCGAGAACGG
.....
+2  Q  S  C  A  V  Q  W  L  I  L  L  E  N  V  C  V  I  S  I  L  N  L  S  C  L  L  Q
    -----------------------------------------------------------------------------------------
+1 P  E  L  C  S  A  V  A  D  S  I  R  E  R  M  R  Y  L  H  P
    ----------------------------------------------------------->
401 CAGAGCTGTG CAGTGCAGTG GCTGATTCTA TTAGAGAACG TATGCGTTAT CTCCATCCTT AATCTCAGTT GTTTGCTTCA
    GTCTCGACAC GTCACGTCAC CGACTAAGAT AATCTCTTGC ATACGCAATA GAGGTAGGAA TTAGAGTCAA CAAACGAAGT
.....
+2   G  P  F  I  F  R  I  Y  S  A  F
    ------------------------------->
481 AGGACCTTTC ATCTTCAGGA TTTACAGTGC ATTCTGAAAG AGGAGACATC AAACAGAATT AGGAGTTGTG CAACAGCTCT
    TCCTGGAAAG TAGAAGTCCT AAATGTCACG TAAGACTTTC TCCTCTGTAG TTTGTCTTAA TCCTCAACAC GTTGTCGAGA
.....
561 TTTGAGAGGA CGCCTAAAGG ACAGGAGAAA AGGTCTTCAA TCGTGGAAAG AAAATTAAAT GTTGTATTAA ATAGATCACC
    AAACTCTCCT CCGGATTTCC TGTCCTCTTT TCCAGAAGTT AGCACCTTTC TTTTAATTTA CAACATAATT TATCTAGTGG
.....
641 AGCTAGTTTC AGAGTTACCA TGTACGTATT CCACTAGCTG GGTTCTGTAT TTCAGTTCTT TCGATACGGC TTAGGGTAAT
    TCGATCAAAG TCTCAATGGT ACATGCATAA GGTGATCGAC CCAAGACATA AAGTCAAGAA AGCTATGCCG AATCCCATTA
.....
721 GTCAGTACAG GAAAAAAACT GTGCAAGTGA GCACCTGATT CCGTTGCCTT GGCTTAACTC TAAAGCTCCA TGTCCTGGGC
    CAGTCATGTC CTTTTTTTGA CACGTTCACT CGTGGACTAA GGCAACGGAA CCGAATTGAG ATTTCGAGGT ACAGGACCCG
.....
801 CTAAAATCGT ATAAAATCTG GA
    GATTTTAGCA TATTTTAGAC CT
    .....
```

Fig 1

```
  1  MNIFLLNLLT EEVRLYSCTP RNFSVSIREE LKRTDTIFWP GCLLVKRCGG
 51  NCACCLHNCN ECQCVPSKVT KKYHEVLQLR PKTGVRGLHK SLTDVALEHH
101  EECDCVCRGS TGG
```

Fig 2

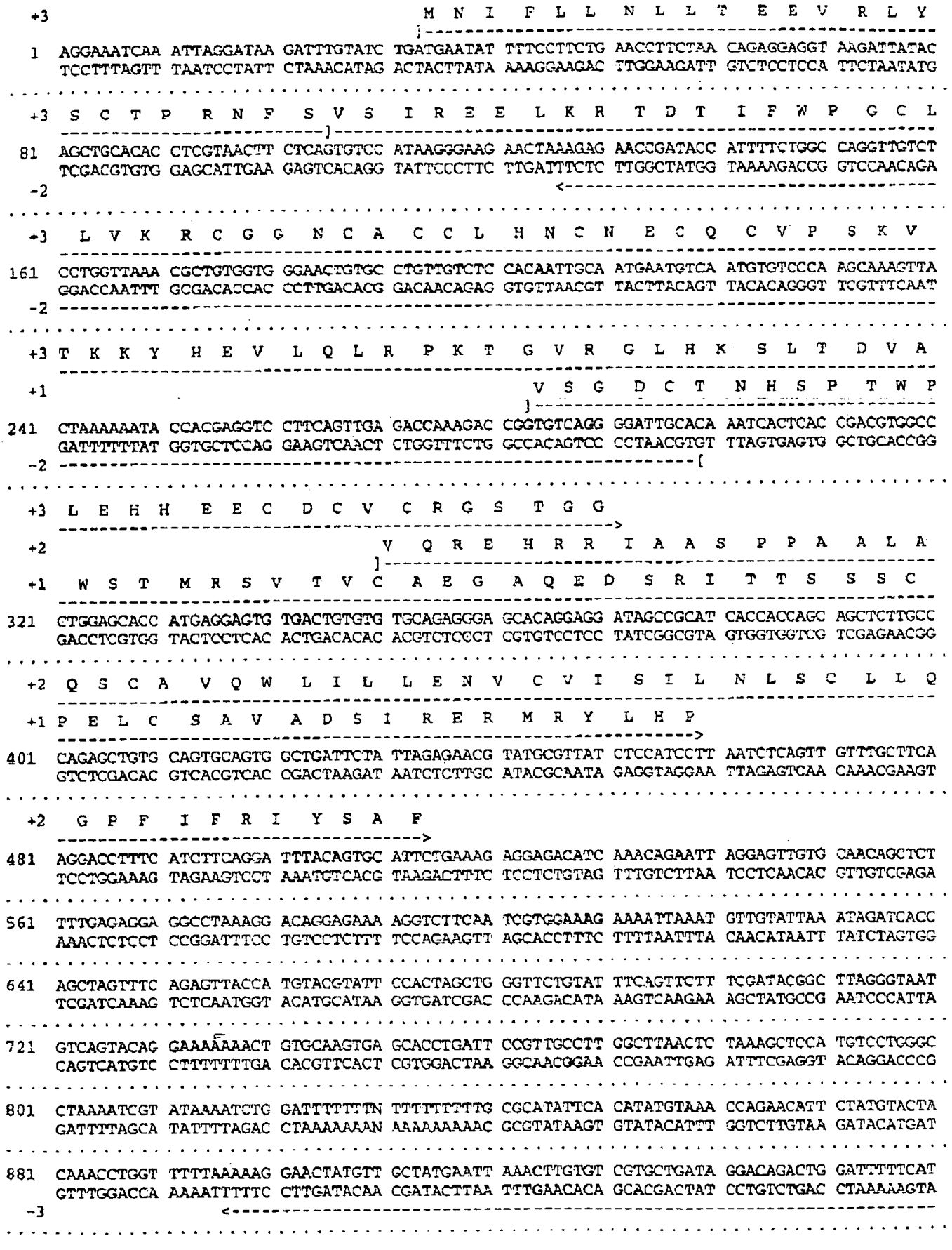
+3 M N I F L L N L L T E E V R L Y
1 AGGAAATCAA ATTAGGATAA GATTTGTATC TGATGAATAT TTTCCTTCTG AACCTTCTAA CAGAGGAGGT AAGATTATAC
TCCTTTAGTT TAATCCTATT CTAAACATAG ACTACTTATA AAAGGAAGAC TTGGAAGATT GTCTCCTCCA TTCTAATATG
+3 S C T P R N F S V S I R E E L K R T D T I F W P G C L
81 AGCTGCACAC CTCGTAACTT CTCAGTGTCC ATAAGGGAAG AACTAAAGAG AACCGATACC ATTTTCTGGC CAGGTTGTCT
TCGACGTGTG GAGCATTGAA GAGTCACAGG TATTCCCTTC TTGATTTCTC TTGGCTATGG TAAAAGACCG GTCCAACAGA
-2
+3 L V K R C G G N C A C C L H N C N E C Q C V P S K V
161 CCTGGTTAAA CGCTGTGGTG GGAACTGTGC CTGTTGTCTC CACAATTGCA ATGAATGTCA ATGTGTCCCA AGCAAAGTTA
GGACCAATTT GCGACACCAC CCTTGACACG GACAACAGAG GTGTTAACGT TACTTACAGT TACACAGGGT TCGTTTCAAT
-2
+3 T K K Y H E V L Q L R P K T G V R G L H K S L T D V A
+1 V S G D C T N H S P T W P
241 CTAAAAAATA CCACGAGGTC CTTCAGTTGA GACCAAAGAC CGGTGTCAGG GGATTGCACA AATCACTCAC CGACGTGGCC
GATTTTTTAT GGTGCTCCAG GAAGTCAACT CTGGTTTCTG GCCACAGTCC CCTAACGTGT TTAGTGAGTG GCTGCACCGG
-2
+3 L E H H E E C D C V C R G S T G G
+2 V Q R E H R R I A A S P P A A L A
+1 W S T M R S V T V C A E G A Q E D S R I T T S S S C
321 CTGGAGCACC ATGAGGAGTG TGACTGTGTG TGCAGAGGGA GCACAGGAGG ATAGCCGCAT CACCACCAGC AGCTCTTGCC
GACCTCGTGG TACTCCTCAC ACTGACACAC ACGTCTCCCT CGTGTCCTCC TATCGGCGTA GTGGTGGTCG TCGAGAACGG
+2 Q S C A V Q W L I L L E N V C V I S I L N L S C L L Q
+1 P E L C S A V A D S I R E R M R Y L H P
401 CAGAGCTGTG CAGTGCAGTG GCTGATTCTA TTAGAGAACG TATGCGTTAT CTCCATCCTT AATCTCAGTT GTTTGCTTCA
GTCTCGACAC GTCACGTCAC CGACTAAGAT AATCTCTTGC ATACGCAATA GAGGTAGGAA TTAGAGTCAA CAAACGAAGT
+2 G P F I F R I Y S A F
481 AGGACCTTTC ATCTTCAGGA TTTACAGTGC ATTCTGAAAG AGGAGACATC AAACAGAATT AGGAGTTGTG CAACAGCTCT
TCCTGGAAAG TAGAAGTCCT AAATGTCACG TAAGACTTTC TCCTCTGTAG TTTGTCTTAA TCCTCAACAC GTTGTCGAGA
561 TTTGAGAGGA GGCCTAAAGG ACAGGAGAAA AGGTCTTCAA TCGTGGAAAG AAAATTAAAT GTTGTATTAA ATAGATCACC
AAACTCTCCT CCGGATTTCC TGTCCTCTTT TCCAGAAGTT AGCACCTTTC TTTTAATTTA CAACATAATT TATCTAGTGG
641 AGCTAGTTTC AGAGTTACCA TGTACGTATT CCACTAGCTG GGTTCTGTAT TTCAGTTCTT TCGATACGGC TTAGGGTAAT
TCGATCAAAG TCTCAATGGT ACATGCATAA GGTGATCGAC CCAAGACATA AAGTCAAGAA AGCTATGCCG AATCCCATTA
721 GTCAGTACAG GAAAAAAACT GTGCAAGTGA GCACCTGATT CCGTTGCCTT GGCTTAACTC TAAAGCTCCA TGTCCTGGGC
CAGTCATGTC CTTTTTTTGA CACGTTCACT CGTGGACTAA GGCAACGGAA CCGAATTGAG ATTTCGAGGT ACAGGACCCG
801 CTAAAATCGT ATAAAATCTG GATTTTTTTN TTTTTTTTTG CGCATATTCA CATATGTAAA CCAGAACATT CTATGTACTA
GATTTTAGCA TATTTTAGAC CTAAAAAAAN AAAAAAAAAC GCGTATAAGT GTATACATTT GGTCTTGTAA GATACATGAT
881 CAAACCTGGT TTTTAAAAAG GAACTATGTT GCTATGAATT AAACTTGTGT CGTGCTGATA GGACAGACTG GATTTTTCAT
GTTTGGACCA AAAATTTTTC CTTGATACAA CGATACTTAA TTTGAACACA GCACGACTAT CCTGTCTGAC CTAAAAAGTA
-3

Fig 3

```
 961  ATTTCTTATT AAAATTTCTG CCATTTAGAA GAAGAGAACT ACATTCATGG TTTGGAAGAG ATAAACCTGA AAAGAAGAGT
      TAAAGAATAA TTTTAAAGAC GGTAAATCTT CTTCTCTTGA TGTAAGTACC AAACCTTCTC TATTTGGACT TTTCTTCTCA
   -3 ----------------------------------------------------------------------------------

1041  GGCCTTATCT TCACTTTATC GATAAGTCAG TTTATTTGTT TCATTGTGTA CATTTTTATA TTCTCCTTTT GACATTATAA
      CCGGAATAGA AGTGAAATAG CTATTCAGTC AAATAAACAA AGTAACACAT GTAAAAATAT AAGAGGAAAA CTGTAATATT
   -3 -------------{

1121  CTGTTGGCTT TTCTAATCTT GTTAAATATA TCTATTTTTA CCAAAGGTAT TTAATATTCT TTTTTATGAC AACTTAGATC
      GACAACCGAA AAGATTAGAA CAATTTATAT AGATAAAAAT GGTTTCCATA AATTATAAGA AAAAATACTG TTGAATCTAG

1201  AACTATTTTT AGCTTGGTAA ATTTTTCTAA ACACAATTGT TATAGCCAGA GGAACAAAGA TGATATAAAA TATTGTTGCT
      TTGATAAAAA TCGAACCATT TAAAAAGATT TGTGTTAACA ATATCGGTCT CCTTGTTTCT ACTATATTTT ATAACAACGA

1281  CTGACAAAAA TACATGTATT TCATTCTCGT ATGGTGCTAG AGTTAGATTA ATCTGCATTT TAAAAAACTG AATTGGAATA
      GACTGTTTTT ATGTACATAA AGTAAGAGCA TACCACGATC TCAATCTAAT TAGACGTAAA ATTTTTTGAC TTAACCTTAT

1361  GAATTGGTAA GTTGCAAAGA CTTTTTGAAA ATAATTAAAT TATCATATCT TCCATTCCTG TTATTGGAGA TGAAAATAAA
      CTTAACCATT CAACGTTTCT GAAAAACTTT TATTAATTTA ATAGTATAGA AGGTAAGGAC AATAACCTCT ACTTTTATTT

1441  AAGCAACTTA TGAAAGTAGA CATTCAGATC CAGCCATTAC TAACCTATTC CTTTTTTGGG GAAATCTGAG CCTAGCTCAG
      TTCGTTGAAT ACTTTCATCT GTAAGTCTAG GTCGGTAATG ATTGGATAAG GAAAAAACCC CTTTAGACTC GGATCGAGTC

1521  AAAAACATAA AGCACCTTGA AAAAGACTTG GCAGCTTCCT GATAAAGCGT GCTGTGCTGT GCAGTAGGAA CACATCCTAT
      TTTTTGTATT TCGTGGAACT TTTTCTGAAC CGTCGAAGGA CTATTTCGCA CGACACGACA CGTCATCCTT GTGTAGGATA

1601  TTATTGTGAT GTTGTGGTTT TATTATCTTA AACTCTGTTC CATACACTTG TATAAATACA TGGATATTTT TATGTACAGA
      AATAACACTA CAACACCAAA ATAATAGAAT TTGAGACAAG GTATGTGAAC ATATTTATGT ACCTATAAAA ATACATGTCT

1681  AGTATGTCTC TTAACCAGTT CACTTATTGT ACCTGG
      TCATACAGAG AATTGGTCAA GTGAATAACA TGGACC
```

Fig 3 (cont'd)

```
  1  MNIFLLNLLT EEVRLYSCTP RNFSVSIREE LKRTDTIFWP GCLLVKRCGG
 51  NCACCLHNCN ECQCVPSKVT KKYHEVLQLR PKTGVRGLHK SLTDVALEHH
101  EECDCVCRGS TGG
```

Figure 4

>3993180H1 LUNGNON03 INCYTE
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GCATC[illegible]CACCAGCAGCTCTTGCCCAGAGCTGTGCAGTGCAGTGGCTGATTCTATTAGAGAACGTATGCGTTATCTCCAT
CCTTAATCTCAGTTGTTTGCTTCAAGGACCTTTCATCTTCAGGATTTACAGTGCATTCTGAAAGAGGAGACATCAAACAG
AATTAGGAGTTGTGCAACAGCTCTTTTGAGAGGAGGCTAAAGGACAGGAGAANAGGTCTT
>3510192H1 CONCNOT01 INCYTE
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>3979767H1 LUNGTUT08 INCYTE
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>3733565H1 SMCCNOS01 INCYTE
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AAATGTTGTATNAAATNGATCACCAGCTAGTTTCAGAGTTACCATGTACGTATTCCACTAGCTGGGNCNGTATTCAGTCT
TTCGGAACGGCTTAGGGTAATGTCAGTACAGGANAAAAACTGTGCAGTGAG
>3554223H1 SYNONOT01 INCYTE

file: short_est_mples

Fig 5

```
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   ACGGCTTAGGGTAATGTCAGTACAGGAAAAAAACTGTGCAAGTGAGCACCTGATTCCGTTGCCTTGGCTTAACTCTAAAG
   CTCC  TCCTGGGCCTAAAATCGTATAAAATCTGGATTTTTTTNTTTTTTTTTGCGCATATTCACATATGTAAACCAGN
79 ACATTCTATGTACNACAAACCTGGTTTTTAAAAAGGAAC
80 >4507477H1       OVARTDT01       INCYTE
81 GGCTAGTTTCAGAGTTACCATGTACGTATTCCACTAGCTGGGTTCTGTATTTCAGTTCTTTCGATACGGCTTAGGCTAAT
82 GTCAGTACAGGAAAAAAACTGTGCAAGTGAGCACCTGATTCCGTTGCCTTGCTTAACTCTAAAGCTCCATGTCCTGGGCC
83 TAAAATCGTATAAAATCTGGA
84 >4163378H1       BRSTNOT32       INCYTE
85 AATAGATCACCAGCTAGTTTCAGAGTTACCATGTACGTATTCCACTAGCTGGGNTCTGTATTTCAGTTCCTTTCGATACG
86 GCTTAGGGTAATGTCAGTACAGGAAAAAAGCTGTGCAAGTGAGCACCTGATTCCGTTGCCTTGCTTAACTCTAAAGCTCC
87 ATGTCCTGGGCCTAAAATCGTATA
```

Fig 5 (cont'd)

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1  >2054675H1       BEPINOT01       INCYTE
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4  TATCGATAAGTCAGTTTATTTGTTTCATTGTGTACATTTTTATATTCTCCTTTTGACATTATAACTGTTGGCTTTTCTAA
5  TCTTGTTAAATATATCTATTTTTACCAAAGGTATTTAATATTCTTTTTTA
6  >3993180H1       LUNGNON03       INCYTE
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9  CCTTAATCTCAGTTGTTTGCTTCAAGGACCTTTCATCTTCAGGATTTACAGTGCATTCTGAAAGAGGAGACATCAAACAG
10 AATTAGGAGTTGTGCAACAGCTCTTTTGAGAGGAGGCTAAAGGACAGGAGAANAGGTCTT
11 >3510192H1       CONCNOT01       INCYTE
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15 TCAGAGTTACCATGTACGTATTCCACTAGCTGGGTTCTGTATTT
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18 GTAAATTTTTCTAAACACAATTGTTATAGCCAGAGGAACAAAGATGATATAAAATATTGTTGCTCTGACAAAAATACATG
19 TATTTCATTCTCGTATGGTGCTAGAGTTAGATTAATCTGCATTTTAAAAAACTGAATTGGAATAGAATTGGTAAGTTGCA
20 AAGACTTTTTGANAATAATTAAATTATCATATCTTCCATTCCTGTTATTGGGGGAGAAAAT
21 >2559870H1       ADRETUT01       INCYTE
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23 TGAGGAGTGTGACTGTGTGTGCAGAGGGAGCACAGGGGGATAGCCGCATCACCACCAGCAGCTCTTGCCCAGAGCTGTGC
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29 ACTTTATCGATAAGTCAGTTTATTTGTTTCATTGTGTACATTTTTATATTCTCCTTTTGACATTATAACTGTTGGCTTTC
30 TAATCTGTTAAATATATCTATTTTTACCAAAGGTATTTAATATTCTTT
31 >3979767H1       LUNGTUT08       INCYTE
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65 ACTAAAAAATACCACGAGGTCC
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74 AAGTTGCAAAGACTTTTTGAAAATAATTAAATTATCATATCTTCCATTCCTGTTATTGGAGATGAAAATAAAAAGCAACT
75 TATGANAGTAG
```

long - est. mfas

Fig 6

```
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Fig 6 (cont'd)

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VEGFE2	GTTTGATGAAAGATTTGGGCTTG	23
VEGFE3	TTTCTAAAGGAAATCAAATTAG	22
VEGFE4	GATAAGATTTGTATCTGATG	20
VEGFE5	GATGTCTCCTCTTTCAG	17
VEGFE6	GCACAACTCCTAATTCTG	18
VEGFE7	AGCACCTGATTCCGTTGC	19
VEGFE8	TAGTACATAGAATGTTCTGG	20
VEGFE9	AAGAGACATACTTCTGTAC	19
VEGFE10	CCAGGTACAATAAGTGAACTG	21

Fig. 7

Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure

Receipt in the case of an original deposit issued pursuant to Rule 7.1 by the International Depositary Authority BCCM™/LMBP identified at the bottom of next page

***International* Form BCCM™/LMBP/BP/4/99-23**

To : Name of the depositor : Janssen Pharmaceutica N.V.

Address : Turnhoutseweg 30
B-2340 Beerse
Belgium

I. Identification of the microorganism:

I.1 Identification reference given by the depositor:

VEGF-X CUB PET22b

I.2 Accession number given by the International Depositary Authority:

LMBP 3991

II. Scientific description and/ r proposed tax n mic designation

The microorganism identified under I above was accompanied by:

(mark with a cross the applicable box(es))

– a scientific description	yes ☒	no ☐
– a proposed taxonomic designation	yes ☐	no ☒

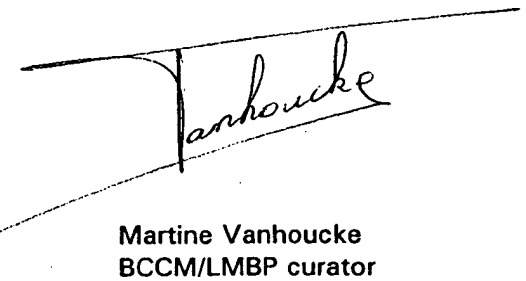
III. Receipt and acceptance

This International Depositary Authority accepts the microorganism identified under I above, which was received by it on (date of original deposit) : December 20, 1999

IV. International Depositary Authority

Belgian Coordinated Collections of Microorganisms (BCCM™)
Laboratorium voor Moleculaire Biologie - Plasmidencollectie (LMBP)
Universiteit Gent
K.L. Ledeganckstraat 35
B-9000 Gent, Belgium

Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s):



Date : January 12, 2000

Martine Vanhoucke
BCCM/LMBP curator